β MHC gene is extremely highly conserved at the amino acid level in both head and rod regions and even neutral polymorphisms appear to be rare.

1029-163 Trophic Effect of Angiotensin II in Rat Neonatal Cardiomyocytes are Caused by Endothelin and Non-Myocyte Cells

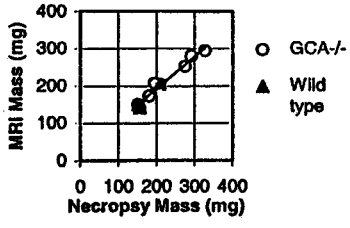
K. Pönicke, I. Heinroth-Hoffmann, K. Becker, O.-E. Brodde. *University of Halle, Germany*

Angiotensin II (ANG II) and endothelin (ET) are known to be potent trophic stimuli in various cells including cardiomyocytes. To further characterize these effects we studied, in isolated rat neonatal cardiomyocytes, the effects of the AT_1-receptor (R) antagonist losartan and the ET_A-R antagonist BQ-123 on ANG II- and ET-1-induced inositol phosphate (IP) formation and protein synthesis (as determined by ^{3}H-phenylalanine incorporation). ET's (0.1–1000 nM, ET-1≫ET-3) concentration-dependently increased IP-formation (max. increase: 130% above basal) and protein synthesis (max. increase: 60% above basal). These effects were antagonized by 1 μM BQ-123 but not by 1 μM losartan. Binding studies with [^{125}I]ET-1 revealed a homogeneous class of ET_A-R in the cardiomyocytes. Pretreatment of the cells with pertussis toxin (PTX, 500 ng/ml for 20 h) did not affect IP-formation but reduced protein synthesis by about 40%. ANG II (0.1–1000 nM) increased IP-formation and protein synthesis to a much lesser extent than ET (max. increases: 30% above basal); these ANG II effects were inhibited by 1 μM losartan but also by 1μM BQ-123 indicating that ET-1 may be involved. In well-defined cultures of cardiomyocytes (not contaminated with non-myocyte cells [NMC]) ANG II failed to stimulate IP-formation and protein synthesis while ET's effects were unaltered. Addition of NMC's to the medium restored the ANG II effects. We conclude a) that in rat neonatal cardiomyocytes ET-1 induces protein synthesis by an, at least partly, PTX-sensitive pathway, and b) that the trophic effect of ANG II in rat neonatal cardiomyocytes is brought about via local ET-1 secretion upon AT_1-R stimulation in cardiac NMC's.

1029-164 Magnetic Resonance Imaging Accurately Estimates Cardiac Mass in a Transgenic Mouse Model of Hypertrophy

F. Franco, S. Dubois, M. Sander, R.M. Peshock, R.V. Shohet. *The University of Texas, Southwestern Medical Center, Dallas, TX, USA*

Transgenic mice with a dysfunctional guanylyl cyclase-a gene (GCA–/–) are unable to transduce the signals from atrial naturetic peptide and thus develop hypertension. We used magnetic resonance imaging (MRI) to assess hypertensive cardiac hypertrophy in these animals, using their wild-type sibs as controls. Mice were anesthetized with serial intraperitoneal injections of avertin and gated multislice, multiphase, cine MRI was done at 1.5 T using a conventional imaging system (1.8 mm slices, 196 μ × 250 μ in-plane resolution, field echo sequence). We used Simpson's rule to estimate myocardial mass from 4–5 short axis images. Correlation with heart weight at necropsy was excellent (LV_{MRI} = 0.87 × $LV_{Necropsy}$ +21 mg, r^2 = 0.97). By MRI GCA–/– mass was significantly different when compared to isogenic controls (GCA–/–: 246 ± 42 mg (n = 7) vs. controls: 166 ± 26 mg (n = 3), p < 0.05). Ejection fraction was similar in the two groups (0.72 vs 0.67, p = NS).



In conclusion, MRI allows non-invasive assessment of murine cardiac hypertrophy and will be useful in longitudinal studies of the effects of genetic or pharmacologic manipulation on cardiac hypertrophy and function.

1029-165 Cardiac-Specific Overexpression of Tumor Necrosis Factor-α Causes Lethal Myocarditis in Transgenic Mice

T. Kubota, C.F. McTiernan, C.S. Frye, A.J. Demetris, A.M. Feldman. *University of Pittsburgh, Pittsburgh, PA, USA*

Tumor necrosis factor (TNF)-α, a proinflammatory cytokine with negative inotropic effects, can be detected in myocardium with end-stage heart failure, after endotoxin administration, and during transplant rejection. Various studies suggest that TNF-α participates in the pathogenesis of cardiac dysfunction. To test this hypothesis, we made a transgenic mouse model which selectively overexpresses TNF-α in cardiomyocytes. A transgene construct was made containing the murine α-myosin heavy chain promoter and the coding sequence of murine TNF-α, followed by the SV40 T antigen intron and polyadenylation signals. Injection of this construct into fertilized eggs yielded 3 transgenic mice, all of which died spontaneously before the completion of weaning. Gross pathological analysis of these mice demonstrated a decrease in body weight with markedly increased heart weight. Histological examination of the heart revealed a substantial, diffuse lymphohistocytic inflammatory infiltrate, associated with interstitial edema. Reverse transcriptase polymerase chain reaction showed that the transgene was expressed in the heart. Enzyme-linked immunosorbent assay demonstrated a substantial amount of TNF-α protein in the transgenic heart. In conclusion, overexpression of TNF-α in the heart leads to severe myocarditis and cardiomegaly. These results support the hypothesis that myocardial expression of TNF-α can contribute to the pathogenesis of cardiac dysfunction.

1029-166 Different Molecular Changes in the β-Adrenergic Signal Transduction Pathway in Primary and Secondary Cardiac Hypertrophy

U. Schotten, C. Schumacher, S. Kulka, M. Sigmund, F. Schöndube [1], P. Hanrath. *Medical Clinic I, Aachen, Germany, [1] Dept. of Thoracic and Cardiovascular Surgery, RWTH Aachen, Germany*

In primary cardiac hypertrophy due to hypertrophic obstructive cardiomyopathy (HOCM) the myocardial β-adrenergic signal transduction is desensitized. The aim of this study was to investigate, whether changes in the myocardial β-adrenoceptors (βAR) and GTP-binding proteins are different in primary and secondary myocardial hypertrophy. *Methods:* Hypertrophied septal myocardium was obtained from patients undergoing operation due to HOCM or severe aortic valve stenosis (AoSt). All patients of both groups showed normal left ventricular pump function. Nonfailing myocardial specimens (NF) were from multiorgan donors, whose hearts could not be transplanted. βAR density (Bmax) was measured with ^{125}I-Iodocyanopindolol (ICYP) binding. For βAR-subtype discrimination ICYP was displaced with a β1-adrenoceptor selective antagonist. Determination of alpha subunits of the stimulatory (Gs 52 kDa; 45 kDa not shown) and inhibitory (Gi-2) G proteins was done by immunoblotting with selective antibodies and γ-counting after ^{125}I-Protein A incubation. *Results:* Bmax = maximal ICYP-binding, β1 and beta;2 = βAR-subtypes (in fmol/mg protein); Gs and Gi in 1000 cpm/mg protein. Values are means ± SEM; p < 0.05: $^+$HOCM (n = 9) or AoSt (n = 8) vs NF (n = 4); *AoSt vs HOCM.

	Bmax	β1	β2	Gs (52 kDa)	Gi-2
HOCM	44 ± 4$^+$	24 ± 3$^+$	20 ± 2	11 ± 1	9 ± 1*
AoSt	38 ± 4$^+$	24 ± 3$^+$	15 ± 2	16 ± 2^{+*}	6 ± 0.5
NF	70 ± 7	51 ± 6	19 ± 2	10 ± 1	6 ± 1

β1-AR were selectively down-regulated in HOCM as well as in AoSt. Whereas in HOCM the inhibitory Gi-2 was increased, in AoSt the stimulatory Gs was increased. *Conclusions:* In HOCM myocardial βAR and G proteins are changed towards desensitization of the β-adrenergic signal transduction pathway whereas they are changed counteractively in secondary myocardial hypertrophy due to AoSt. The changes in the β-adrenergic signal transduction pathway in hypertrophied human myocardium depend upon the etiology of the hypertrophy.

1030 Neural Control of Cardiac Function in Hypertension

Tuesday, March 18, 1997, 3:00 p.m.–5:00 p.m.
Anaheim Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

1030-45 Relationship of QT Dispersion to LVH in Patients With Hypertension

M.W. Jacocks, A.L. Hinderliter, D.A. Tate, P.W. Willis, IV, W.E. Cascio, L.S. Gettes. *University of North Carolina, Chapel Hill, NC, USA*

In patients with hypertension, LVH is associated with an increased risk of sudden cardiac death. The mechanism is incompletely understood. Dispersion of the QT interval is an index of repolarization inhomogeneity, and increased QT dispersion may indicate enhanced susceptibility to ventricular arrhythmias.

To determine the relationship between QT dispersion and LV mass, we